microadenomas, and, therefore, a low risk category was identified which was comprised of galactorrheic women who were menstruating regularly and had normal PRL levels. In galactorrheic patients who gave a history of either oligomenorrhea or amenorrhea, no such category could be identified because nine patients with normal serum levels of PRL were found to have radiologic evidence compatible with having a pituitary microadenoma. It is clear that galactorrheic patients with amenorrhea, low serum estrogen levels and elevated serum PRL concentrations have a high incidence of pituitary microadenomas. In our series of 42 such patients, 29 (69 percent) had microadenomas.

Utilizing all this information it has been possible to construct an outline for investigating and managing patients with galactorrhea (Figure 27). This approach utilizes a single measurement of serum TSH and PRL in conjunction with the menstrual history and use of polytomograph. The various therapeutic modalities available for treating prolactin-secreting microadenomas or macroadenomas have been discussed recently.[44]

Hirsutism in Adolescents

GLENN D. BRAUNSTEIN, MD*

Normal Hair Growth

HAIR MAY BE CLASSIFIED into three categories: asexual, ambisexual and sexual.[45] Asexual hair, the growth and distribution of which are independent of sex or gonadal steroid production, includes the scalp, eyelash, eyebrow and lumbosacral triangle hair. Ambisexual hair grows in response to low levels of adrenal and gonadal androgens and occurs in both sexes. Thus pubic and axillary hair, hair on limbs and, to a lesser extent, the hair extending along the linea alba from the umbilicus to the pubic triangle fall into this category. Sexual hair is normally restricted to males and is dependent upon the androgen concentration. Beard, moustache, nasal-tip, pinnea, back and chest hair are examples of androgen sensitive sexual hair.[45] Hirsuitism may, therefore, be defined as excessive sexual hair growth in the androgen sensitive areas of the body in a phenotypic female.

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A variety of factors are involved in growth of sexual hair. These include the sensitivity of hair follicles to circulating androgens, the ability of hair follicles to convert weak androgens or androgen precursors to more potent androgens, the potency of the androgens that the hair follicles are exposed to, the location of the hair and the duration of exposure of the follicle to androgens.[46] Sexual hair begins as vellus or fine, lightly pigmented lanugo-type hair which upon exposure to sufficient quantities of androgens may be irreversibly converted to a thick, darkly pigmented, deeply rooted terminal hair. Once a terminal hair is formed it seems that very little androgen is required to maintain hair growth.[47] Terminal sexual hairs go through a growth cycle that varies between two and four years, and at the end of the cycle the hair shaft falls out and new hair formation may take place.[48]

Androgen Metabolism in Women

In a nonpregnant woman, approximately 25 percent of the serum testosterone is derived from direct adrenal secretion, approximately 25 percent from ovarian secretion and 50 percent is derived from peripheral or extraglandular conversion of the 17-ketosteroid androgen precursors, primarily dehydroepiandrosterone (DHEA) (90 percent from adrenal glands, 10 percent from ovaries) and Δ^4-androstenedione (50 percent from adrenal glands, 50 percent from ovaries).[49-51] In addition to testosterone, three other androgens which, like testosterone, are 17β-hydroxysteroids, are important in women. These androgens are Δ^5-androstenediol, dihydrotestosterone and 3 α-androstanediol, and are almost exclusively derived from the extraglandular conversion of DHEA, androstenedione and testosterone.[50] If one takes into account the average plasma concentration of each of these androgens, their relative androgenicity and the amount that exists in the unbound biologically active state in the blood, then an androgenicity index may be computed.[50,52] Therefore, approximately half of the total androgenic activity in the plasma of a normal woman is due to testosterone, while the other three 17β-hydroxysteroids contribute to the remaining androgen activity.

Approximately 99 percent of the circulating androgens are bound to serum proteins, while the remaining 1 percent is unbound and is capable of entering the androgen target tissues to exert its biologic action. The two serum proteins that bind

androgens are testosterone-estradiol-binding globulin (TeBG; sex steroid binding globulin), a protein with high affinity for androgens, and albumin which has a low affinity for androgens but greater binding capacity. The synthesis of TeBG by the liver is increased by estrogen administration, pregnancy and hyperthyroidism, while androgens, some progestogens and glucocorticoids decrease TeBG synthesis.[49-51] Men normally have lower TeBG levels than women and the percent of the androgens that are free is greater in men than women. The TeBG levels in hirsute women are between those found in normal men and women and, therefore, the percentage of unbound androgen is greater than normal.[49-51] This combined with the increased testosterone production rate in hirsute women[49] accounts for the observed increase in the absolute concentration of free testosterone seen in 60 percent to 100 percent of hirsute women.[52-54]

Classification of Hirsutism

Cases of hirsutism may be classified on a clinical basis into those patients with androgen-sensitive excessive hair growth alone and those with associated virilization. Virilization or defeminization includes hirsutism and acne with clinical evidence of a more severe degree of androgenization including malodorous perspiration, deepening of the voice due to enlargement of the larynx (an androgen-sensitive organ), male muscle pattern and body contour development, increased libido, clitoral hypertrophy (greater than 1 cm in diameter) and temporal hair recession. Studies carried out on hirsute and virilized patients have shown that testosterone production rates correlate closely with the clinical manifestations of androgen excess, indicating that hirsutism is on a continuum with virilization.[49] However, for clinical purposes, patients may be divided into those who have simple hirsutism without virilization and and those with hirsutism associated with virilization (Table 4).

Hirsutism Without Virilization

In approximately 99 percent of patients with simple hirsutism there is either no discernible pathologic condition or a benign underlying condition.[55,56] The frequency of hirsutism varies with the population studied. McKnight[57] noted that 9 percent of 440 women students at the University of Wales were hirsute in comparison to their peers, while Ferriman and co-workers[58] found that 10 percent to 15 percent of unselected female patients in hospital and in the 15 to 44 year age range had hirsutism.

The sensitivity of the hair follicles to androgen stimulation is in part under the influence of genetic control. Consequently, daughters of hirsute women have an increased likelihood of being hirsute.[59] In addition to the immediate familial influences, the racial background of the individual person also influences sexual hair growth. Women from the Mediterranean area have more sexual hair on the average than Scandinavian women.[55,60,61] Similarly, Caucasians are more hirsute than Mongoloids.[55] Women with familial or racial hirsutism characteristically note the excessive hair growth beginning around the time of menarche, usually have normal cyclic menses, and generally have normal plasma or serum androgen levels.

Patients without a family history or racial susceptibility for hirsutism and who are not found to have a pathologic problem responsible for their

TABLE 4.—*Causes of Hirsutism in Adolescent Women*

- Without Virilization
  - Normal persons
    - Familial or racial
    - Idiopathic
    - Drugs
    - Pregnancy
  - Pathologic conditions
    - Ovarian disorders
      - Polycystic ovary disease
      - Hyperthecosis
    - Adrenal disorders
      - Bilateral adrenocortical hyperplasia
    - Thyroid disorders
      - Hypothyroidism
    - Pituitary disorders
      - Acromegaly or gigantism
    - Miscellaneous
      - Central nervous system injury
      - ? Emotional stress
      - Malnutrition
      - Porphyria
- With Virilization
  - Normal persons
    - Androgen administration
  - Pathologic conditions
    - Ovarian disorders
      - Polycystic ovary disease
      - Virilizing ovarian tumors
    - Adrenal disorders
      - Congenital adrenal hyperplasia
      - Adrenal carcinoma
      - Virilizing adrenal adenoma
    - Male pseudohermaphroditism

excessive hair growth are classified as having idiopathic hirsutism. Again this disorder begins during the pubertal years with a slowly progessive increase in hair growth during the second and third decades. Menstrual cycles may be normal or abnormal. Those patients with abnormal menstrual cycles generally tend to be more obese and have greater elevations of serum androgens then those with normal cycles.[62] Total serum testosterone is elevated in 33 percent to 82 percent of these patients,[52-54,63-67] while testosterone production rates are increased in over 90 percent.[49] In most instances the ovaries are the source of the excessive androgen production in patients with idiopathic hirsutism.[68]

Pregnancy may be associated with excessive facial, periareolar, intramammary and extremity hair.[69] This is usually noted during the first trimester and may be due to excessive ovarian androgen secretion. This form of hirsutism usually remits antepartum or following delivery.

A number of drugs may cause iatrogenic hirsutism. Diphenylhydantoin may induce hair growth on the trunk, face and extensor surfaces of the extremities, within two to three months after beginning therapy.[70] The increased collagen deposition in the skin and increased cutaneous vascularity may be of etiologic importance. Diazoxide, minoxidil, glucocorticoids, ACTH, anabolic steroids and C-19 progestogens, such as norethindrone and norethynodrel, may be associated with hirsutism.[55] Withdrawal of the offending drug usually results in a disappearance of the excessive hair.

The most frequent pathologic cause of hirsutism without virilization is polycystic ovary disease. Hirsutism occurs in approximately half of the patients with this disorder.[71] These patients may also have obesity, oligomenorrhea or amenorrhea, and involuntary infertility. The hirsutism characteristically begins at the time of puberty and is often slowly progressive. Serum testosterone levels may be normal or elevated, but the testosterone production rate is usually increased.[49] The primary source of the androgens is the ovaries, although combined ovarian and adrenal androgen secretion has been noted.[72] Ovarian hyperthecosis clinically resembles polycystic ovary disease, although the pathologic changes in the ovaries are somewhat different.

Cushing disease with bilateral adrenocortical hyperplasia may be associated with a mild degree of hirsutism, probably due to the combined effects of ACTH-induced adrenal androgen secretion and the reduced levels of TeBG that result from excessive quantities of glucocorticoids.[73] Similarly, reductions in TeBG have been found in patients with hypothyroidism[74] and acromegaly.[75] In each of these disorders hirsutism is not the primary complaint and the other physical stigmata of the underlying endocrinopathy are usually readily apparent.

Although hirsutism is occasionally noted following head injuries, psychogenic stress and disorders associated with starvation such as in anorexia nervosa, the pathophysiologic alterations responsible for the hair growth have not been defined.[71] Hirsutism may occur in the sun exposed areas in patients with porphyria, especially porphyria cutanea tarda.[76] The cause is unclear but may be related to the irritative effects of porphyrin deposition in the skin followed by sunlight exposure.

Hirsutism With Virilization

Hirsutism with virilization is usually due to a significant pathologic disorder. Normal persons given androgens or anabolic steroids may become virilized and some degree of virilization has been noted in approximately 20 percent of the patients with polycystic ovary disease.[77] Rarely, the virilizing forms of congenital adrenal hyperplasia[78] and male pseudohermaphroditism[55] may escape detection until adolescence. Once these conditions are considered and excluded, virilizing ovarian tumors such as arrhenoblastomas, granulosa-theca cell tumors, hilus cell tumors, luteomas of pregnancy, or Krukenberg tumors, and adrenal adenomas or carcinomas are the most likely diagnostic considerations. Both ovarian and adrenal neoplasms present with a rapid onset of hirsutism, menstrual irregularities and virilization because of the secretion of large amounts of androgens or androgen-precursors which are converted to androgens by the peripheral tissues. In addition adrenocortical carcinomas may have signs and symptoms of excessive glucocorticoid and mineralocorticoid production.

Diagnostic Evaluation

In women with simple hirsutism without virilization, a careful family, racial and drug history, and physical examination should be sufficient to allow the diagnosis of familial and drug-induced hypertrichosis, pregnancy, Cushing disease, hypothyroidism, acromegaly, and the miscellaneous

causes of hirsutism. The remaining patients most likely have idiopathic hirsutism or polycystic ovary disease. If menstrual cycles are normal, it is unlikely that the serum androgen levels will be more than minimally elevated. For patients with hirsutism and menstrual irregularities, serum testosterone and luteinizing hormone concentration should be measured. Because of the spontaneous fluctuations in these hormones it is recommended that three blood specimens be obtained 20 minutes apart and the serum separated. Two milliliter aliquots of each of the serums may then be combined and a single testosterone and LH measurement made. This allows integration of the hormone levels in order to obtain a more accurate mean hormone concentration in a cost-effective manner. If testosterone concentrations are less than 200 ng per dl no further evaluation is necessary. Normal or slightly elevated serum testosterone levels with normal LH concentrations are compatable with idiopathic or familial hirsutism, while patients who have elevated testosterone and LH levels are most likely to have polycystic ovary disease.

Patients with a rapid onset of virilization require an intensive endocrinologic evaluation. Serum testosterone and dehydroepiandrosterone-sulfate (DHEA-sulfate) levels should be measured. Pronounced elevation of testosterone with normal DHEA-sulfate concentrations indicates the presence of ovarian neoplasm, while elevated testosterone with high DHEA-sulfate levels is usually indicative of an adrenal disorder. A dexamethasone suppression test should be carried out in the latter patients. In patients with congenital adrenal hyperplasia the serum DHEA-sulfate and testosterone concentrations are suppressed after five days of dexamethasone administration (1 mg given orally twice a day for five days) while in patients with virilizing adrenocortical adenoma or carcinoma this does not occur. Pelvic ultrasound, computerized axial tomographic scans of the adrenals, angiography, or adrenal and ovarian vein catheterization with measurement of androgens in the blood from each organ may be useful for determining the location of ovarian and adrenal neoplasms.

Treatment

If a pathologic condition is found to be responsible for the hirsutism or virilization, therapy directed at the primary disorder should be given because in most instances the hirsutism will regress or the rate of hair growth will diminish. For patients with familial or idiopathic hirsutism or polycystic ovary disease two types of therapy, cosmetic and medical, are available.

The cosmetic therapies include bleaching, plucking, wax stripping, shaving, use of chemical depilatories and electrolysis.[48] Bleaches are most useful for lightly pigmented, shallow terminal hairs in the sideburn or moustache areas. Many women utilize plucking or tweezing of moustache or chin hairs. However, this may lead to local infection of the hair follicle and the repeated skin trauma may actually stimulate vellus hairs to be transformed into terminal hairs.[79] In addition, repeated tweezing may alter the direction of the hair follicle which makes subsequent electrolysis difficult. Wax stripping involves the application of molten wax to the skin. After the wax hardens it is removed and the entrapped hairs are pulled out. Adverse effects of this method of mass plucking include a mechanical and occasional chemical dermatitis, skin infections and increased conversion of vellus to terminal hairs. Shaving does not stimulate the formation of new hairs and does not make hairs coarser or darker.[80] It does cut the hair at the thickest portion of the shaft which may result in a stubble as the hair grows out. Therefore, this treatment should be reserved for excessive thigh, lower extremity, abdominal and periareolar hair. Depilatory creams or pastes chemically shave the hairs off at the skin surface and have the same advantages and disadvantages as shaving.[80]

The only cosmetic therapy that results in permanent removal of hair is electrolysis and its variants.[79] Either electrical or high frequency currents are transmitted through a fine needle which has been inserted along the hair shaft into the hair follicle. This results in desiccation of the hair bulb and papilla. Although this has the advantage of permanently destroying the follicle, only 50 percent to 70 percent of the follicles treated are actually destroyed during any treatment session because of technical difficulties. This form of treatment is expensive, time consuming and painful. If the hirsutism is severe, electrolysis should be combined with some form of medical therapy in order to reduce the rate of new hair growth during treatment.

Several types of medical therapy have been advocated for the treatment of hirsutism. Glucocorticoids, usually given as dexamethasone in doses of 0.5 to 0.75 mg orally at night, decrease

the rate of hair growth in 30 percent to 50 percent of patients.[53,81] These doses will suppress the early morning rise in ACTH and hence adrenal androgen production. In addition there is evidence that ovarian androgen and androgen precursor secretion is diminished by this therapy.[68] The major adverse effects of this therapy are appetite stimulation, weight gain and insomnia. Prolonged suppression of the hypothalamic-pituitary-adrenal axis is usually not seen.[82] Birth control pills containing high concentrations of estrogen, such as Ortho-Novum 2 mg tablets or Norinyl 2 mg tablets, effectively reduce the rate of hair growth in approximately half of the patients.[71,83] These agents decrease ovarian and adrenal androgen production and stimulate the liver to synthesize increased quantities of TeBG.[83,84] Because TeBG is the major serum androgen-binding protein the amounts of free or biologically active androgens are reduced. It should be noted that the major adverse effects attributed to birth control pills are due to the estrogen content and, therefore, both physicians and patients must carefully weigh the potential risks of using these agents for treating a cosmetic problem.

Several experimental therapies for hirsutism have been developed. Medroxyprogesterone acetate in a dose of 100 mg given intramuscularly every two weeks or 30 to 40 mg given orally daily has been shown to reduce serum androgen levels by decreasing testosterone production.[85,86] This agent may also interfere with the peripheral action of the androgens at the androgen target organ level.[86] Breakthrough bleeding, menstrual irregularities and increased appetite with weight gain may occur. Spironolactone displaces androgens from their intracelluar binding protein and has recently been shown to reduce excessive hair growth in hirsute women.[87] Another antiandrogen, which has been used extensively in Europe but is not available in the United States, is cyproterone acetate. Like spironolactone, this drug displaces androgens from the receptor proteins in androgen-sensitive tissues. It is 60 percent to 80 percent effective in reducing hair growth but should be given cyclically with estrogens because of the frequently associated menstrual abnormalities.[88,89]

Because of the long (two to four year) cycle of hair growth in the androgen-sensitive areas of the body, patients should be told that at least six months of therapy may be required before a sufficient number of hairs are lost to allow an objective assessment of the therapeutic effects. In addition patients should not be told that the excessive hair will disappear. Rather, it should be emphasized that effective medical therapy will only reduce the rate of hair growth, which when combined with the cosmetic therapies may lead to an acceptable psychosocial result.

The Clinical Consequences of Stilbestrol Exposure *In Utero*

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IN 1971 HERBST and associates[90] described the cases of eight young women with clear cell carcinoma of the vagina exposed to diethylstilbestrol (DES) *in utero*. A Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Women (now the Registry for Research on Hormonal Transplacental Carcinogenesis) was established to centralize data on these patients thereby facilitating rapid dissemination of information on the biological behavior of these tumors and on appropriate therapeutic modalities. At present, the Registry serves as a repository for clinical and pathologic data on more than 330 women with this neoplasm. Reports from the Registry[91,92] and additional publications from other institutions[93-106] have not only substantiated the association of vaginal and cervical clear cell carcinoma with *in utero* DES exposure, but have also shed light on a group of benign lesions resulting in pronounced alterations of the lower genital tract. These alterations include cervical or vaginal ridges and ectopic location of benign glandular epithelium in the vagina (adenosis) and cervix (ectropion).[103-106] There have also been reports suggesting that due to the presence of extensive vaginal adenosis and cervical ectropion in these patients, there may be an increased risk of squamous carcinoma of the vagina and cervix.[107,108] These findings have widespread implications; it has been estimated that several hundred thousand young women were exposed to DES *in utero* between 1945 and 1970 in the United States[109] when DES was used to treat patients with threatened and repeated abortions. This form of therapy was used not only in the

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